

CALCIUM FORMATE FOR USE AS A DIETARY SUPPLEMENT

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. Serial Nos.

09/469,513, filed December 22, 1999 and 09/649,710, filed August 25, 2000.

Both of these documents are incorporated by reference as if set forth fully

5 herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

BACKGROUND OF THE INVENTION

10 A. Calcium Formate as a Phosphate Binder

Phosphorus retention plays a major role in chronic renal failure in the development of both secondary hyperparathyroidism and osteodystrophy.

Bricker, N., S. et al., *Archives of Internal Medicine* 123:543-553 (1969);

Rubini, M.E. et al., *Archives of Internal Medicine* 124:663-669 (1969);

15 Slatopolsky, E., et al., *Journal of Clinical Investigation* 50:492-499 (1971);

Bricker, N.S., *New England Journal of Medicine* 286:1093-1099 (1972);

Slatopolsky, E.S., et al., *Kidney Int.* 2:147-151 (1972).

Antacids are often used to bind dietary phosphorus to prevent phosphorus retention and prevent its absorption. This process is referred to 20 as phosphorus binding and appears to be a chemical reaction between dietary phosphorus and the cation present in the binder compound, which is

usually albumin or calcium. The binding results in the formation of insoluble and unabsorbable phosphate compounds, adsorption of phosphorus ions on the surface of binder particles, or a combination of both.

Presently-used antacids are inefficient at binding phosphorus *in vivo*.

- 5 For example, a recent study by Ramirez, et al., noted that even though aluminum-containing or calcium-containing antacids were administered in large excess, they bound only 19-35 percent of dietary phosphorus. Ramirez, J. A., et al., *Kidney Int.* 30:753-759 (1986). Similar conclusions can be derived from data presented in earlier studies. Kirsner, J. B., *Journal of*
- 10 *Clinical Investigation*, 22:47-52 (1943); Clarkson, E.M., et al., *Clinical Science* 43:519-531 (1972); Cam, J.M., et al., *Clinical Science and Molecular Medicine* 51:407-414 (1976); Man, N.K. et al., *Proceedings of the European Dialysis and Transplantation Association* 12:245-55 (1975).

- Antacids are used widely, often in large quantities, for indigestion, heartburn or peptic ulcer disease. Despite their consumption in large amounts and often over long periods of time, phosphorus depletion is uncommon in these settings. This fact is additional evidence of the inefficiency of antacids as phosphorus binding agents.

- The inefficiency of commonly used phosphorus binders creates a clinical dilemma. The dose of the binder must be increased to control hyperphosphatemia, but increased risk of toxicity of the binder results from the increased dose. This toxicity includes bone disease and aluminum dementia from aluminum-containing antacids and hypercalcemia and soft

tissue calcification from calcium-containing antacids. These risks are particularly problematic in patients with chronic renal disease.

It would be very useful to have a phosphorus binder available which does not have the risks associated with ingestion of presently available binders. The binder should be more efficient in binding phosphorus and, thus, would not have to be consumed in the large quantities necessary, for example, when calcium carbonate-containing compositions are used. Such a phosphorus binder would be particularly valuable for administration to individuals with chronic renal failure, in whom phosphorus retention is a serious concern and the risk of toxicity from consumption of presently-available binders is greater than in individuals in whom kidney function is normal.

U.S. patent 4,870,105 addresses these concerns by disclosing a calcium acetate phosphorus binder. However, it would be advantageous to find a binder with a smaller anion and, hence, a smaller effective dose.

B. Calcium Formate as a Dietary Supplement

Calcium is an abundant element in the human body and plays an important role in many physiological processes. Nutritional and metabolic deficiencies of calcium can have adverse effects, typically manifested through deficiencies in the structure, function and integrity of the skeletal system. The most common calcium-modulated metabolic bone disorder is osteoporosis.

A preferred approach to calcium supplementation is through dietary sources. Dairy products are the major contributors of dietary calcium, as are

green vegetables (e.g. broccoli, kale, turnip greens, Chinese cabbage), calcium-rich tofu, some legumes, canned fish, seeds and nuts. Breads and cereals can contribute significantly to calcium intake.

- Calcium supplements may be the preferred way to obtain
- 5 supplemental calcium. Calcium carbonate is usually recommended for economic reasons. However, calcium carbonate usage requires sufficient gastric acids for its utilization. Some individuals, especially the elderly, may have limited amounts of gastric acid, and achlorhydric patients have little gastric acid. For such cases, calcium carbonate is poorly utilized. Using
- 10 large amounts of calcium carbonate may also lead to constipation and abdominal distention. Calcium lactate or calcium citrate may then be used.

Needed in the art of calcium supplementation is a very soluble calcium supplement with smaller anion and, hence, a smaller effective dose.

SUMMARY OF THE INVENTION

- 15 In one embodiment, the present invention relates to a method of binding phosphorus in the gastrointestinal tract and, thus, reducing phosphorus absorption from the intestine. It also relates to a method of reducing serum phosphate levels because phosphorus bound in the gastrointestinal tract results in lower phosphorus absorption than would
- 20 otherwise occur. It is particularly useful in the treatment and prevention of hyperphosphatemia in individuals with renal disease or other disease in which the ability to excrete phosphorus from the body (e.g., in the urine) is impaired.

The method of the present invention comprises orally administering to an individual a composition which includes calcium formate in sufficient quantity to effectively bind phosphorus, preferably present in food and beverages consumed by the individual, and prevent its absorption in the 5 intestine. In an advantageous form of the invention, the calcium formate is administered at a dose of between 0.5 and 10.0 grams.

The present invention is also a method of using calcium formate as a dietary calcium supplement. The method comprises orally administrating to an individual a composition comprising calcium formate in sufficient quantities 10 to improve calcium balance or retention.

In an advantageous form of the invention, the calcium formate is administered in a dose between 0.5 and 3.0 g/day as a supplement.

The present invention is also a pharmaceutical composition comprising calcium formate in combination with a pharmaceutically acceptable carrier. In 15 a preferred embodiment, the composition comprises 0.5 grams of calcium formate per capsule or tablet. In another preferred embodiment, the composition comprises calcium formate and at least one additional therapeutic ingredient. In a most preferred embodiment, this therapeutic ingredient is a vitamin D compound, typically cholecalciferol.

20 It is a feature of the present invention that the amount of calcium-containing compound sufficient to inhibit gastrointestinal phosphorus absorption is 10% lighter than therapeutically equivalent amounts of previously known calcium acetate compounds.

It is another feature of the present invention that calcium formate may be supplied orally to an individual in order to supplement the individual's calcium intake.

- Other objects, features and advantages of the present invention will 5 become apparent to one of skill in the art after review of the specification and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a calcium formate composition for oral administration to an individual. The composition is useful in reducing 10 phosphorus absorption in the gastrointestinal tract. Calcium formate is shown below to be effective in inhibiting phosphorus absorption when administered orally in *in vivo* tests and has been shown to prevent the absorption of ingested phosphorus at a lower dose than other calcium-containing binders. As a result of these discoveries, calcium formate, alone or in combination with 15 other materials, can be used to bind phosphorus in the gastrointestinal tract, thus reducing the percentage of an amount of phosphorus consumed (i.e., of a given "dose" of phosphorus) which is absorbed. Preferably, this dose would be 0.5 - 10.0 grams when adjusted to doses intended for human patients.

The present invention also relates to a method of inhibiting 20 gastrointestinal phosphorus absorption. The method of the present invention is based on the demonstration that calcium formate is an effective binder of phosphorus when administered orally to an individual. The method comprises orally administering a quantity of calcium formate sufficient to bind

with phosphorus in the gastrointestinal tract. Preferably, this dose is between 10 - 200 milliequivalents of calcium and is preferably present in either tablet or gelatin capsule form. In a most preferable form of the present invention, the oral dose is ingested at mealtimes.

5 As a result of the present invention it is possible to administer calcium formate to reduce absorption of dietary phosphorus, which has the net effect of reducing the risks of adverse effects (e.g., bone disease and secondary hyperparathyroidism) observed in individuals (e.g., chronic renal patients) in whom the ability to excrete phosphorus in the urine is impaired.

10 As used herein, the term "phosphorus" includes phosphorus and phosphate in its various forms (e.g. HPO_4^- , PO_4^{3-} , etc.).

According to the method of the present invention, calcium formate is administered, alone or in combination with other substances (e.g., in a hard gelatin capsule; along with materials necessary to form a tablet or caplet as a delivery vehicle for the calcium formate; or along with a second phosphorus binder or other pharmaceutically useful substance) in sufficient quantities to reduce phosphorus absorption in the gastrointestinal tract. The calcium formate is administered orally, preferably close in time to food and beverage consumption. By "at mealtimes" we mean within 30 minutes of a meal.

20 In one embodiment, 0.5 - 10.0 grams of anhydrous calcium formate (10 - 200 milliequivalents calcium) is taken prior to food consumption (e.g., meal time) and a second dose of 0.5 - 10.0 grams of anhydrous calcium formate is taken after food consumption. The dose or quantity to be taken at a given time varies on an individual-by-individual basis and can be adjusted

as needed (e.g., by monitoring serum concentration of phosphorus and calcium).

In another embodiment of the present invention, calcium formate is administered, alone or in combination with other substances, in sufficient quantities to supplement an individual's calcium intake. The Examples below indicate that calcium formate in quantities between 0.5 and 3.0 g/day are sufficient to improve calcium balance, bone density and calcium retention.

The present invention is also a pharmaceutical composition comprising calcium formate in a pharmaceutically acceptable carrier, wherein the calcium formate is present in an amount between 0.5 - 1.0 grams. In another embodiment, the pharmaceutical composition comprises calcium formate in an amount suitable to inhibit gastrointestinal absorption of phosphorus, provides between 11 and 44 milliequivalents of calcium, and is 10% lighter than the corresponding calcium acetate dose and is the richest form of calcium available. By "corresponding" or "therapeutically equivalent," we mean a dose that is equally effective.

In another embodiment of the present invention, the pharmaceutical composition essentially comprises only calcium formate and at least one pharmaceutically carrier, wherein the calcium formate is present in an amount sufficient to produce between 11 and 44 milliequivalents of calcium. By "essentially comprises" we mean that calcium formate is the only active ingredient in the pharmaceutical composition.

The present invention is also a pharmaceutical composition comprising calcium formate in a pharmaceutically acceptable carrier combined with other

therapeutic agents, preferably a vitamin D compound. Most preferably, the calcium formate is combined with vitamin D is cholecalciferol in a range of 125 IU to 400 IU in a tablet or capsule.

EXAMPLE 1

5 Calcium Formate as a Phosphate Binder in Normal Rats

Table 1

1 Week on Diet				
Group	% Ca Formate	Serum (mg%) (mean±SEM)	Weight	Serum Ca (mg%) (mean±SEM)
10	1	4.96±.48	209±5.5	ND
	2	3.25±.31	229±5.5	ND
	3	2.50±.32	211±6.3	ND
	4	2.5±.20	194±6.5	ND
2 Weeks on Diet				
15	1	5.98±.39	295±4.8	11.4±.20
	2	4.70±.62	211±3.8	14.0±.51
	3	2.7±.24	198±5.2	12.8±.94
	4	2.9±0.8	150±8.0	12.9±1.3

ND=not determined. There were at least 6 rats per group.

20 Five-week-old Sprague Dawley rats were given a synthetic diet containing 0.47% Ca and 0.2% phosphorus for two weeks prior to the addition of calcium formate to the diet. Body weights were measured and blood serum was collected after one or two weeks on calcium formate.

The results of this experiment are tabulated in Table 1. All rats supplied with calcium formate had less serum phosphorus than control rats. There seemed to be little difference in serum phosphorus between rats on 2%

or 3% calcium formate, thus indicating that a saturation binding point had been reached.

EXAMPLE 2

Twenty 15-day-old weanling rats from Holzmann Company were
5 placed on a an adequate synthetic diet called "Diet 11" (Suda, T., et al., J.
Nutr. 100:1049-1052, 1970). This diet is supplemented with vitamins A, D, E
and K as described in that paper. Therefore, these are vitamin D-sufficient
animals.

The animals were then placed on a basal diet that contains 0.02%
10 calcium, i.e. an extremely low calcium diet. These animals served as
controls. Another group were placed on the same diet containing calcium
formate, providing calcium at 0.25% of the diet. Another group was supplied
calcium formate at 0.47% calcium in the diet, and another group was provided
0.47% calcium in the form of calcium carbonate. Growth of the animals
15 reflects the ability of the animals to utilize calcium. Using a growth assay of
this type to illustrate the effectiveness of the calcium salt is supported by
Steenbock, H. and D.C. Herting, *J. Nutr.* 57:449-468, 1955.

Table 2, below, tabulates the results. Referring to Table 2, we
conclude that calcium formate is at least equal to calcium carbonate in ability
20 to supply calcium to experimental rats. In fact, there is a slightly better growth
obtain with 0.25% calcium as the formate in comparison to other treatment
groups. Calcium formate can therefore be used as a dietary supplement to
provide dietary calcium.

Table 2

Average Body Weight in Grams \pm S.E.M for 5 Rats				
	Day	Control Diet (0.02% Ca)	Calcium Formate (0.25% Ca)	Calcium Carbonate (0.47% Ca)
5	7	47.6 \pm 10.8	54.3 \pm 4.0	51.0 \pm 10.6
	14	74 \pm 10.7	84.6 \pm 5.5	78.0 \pm 19
	21	85.6 \pm 10	131.0 \pm 5.7*	127 \pm 11*

*Significantly different from control by Students 't' test. P < 0.001.